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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,125	08/14/2001	Susan Hand-Zimmermann	210121.544	9404

500 7590 01/31/2006

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,125	HAND-ZIMMERMANN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *15* is/are allowed.

6)☐ Claim(s) *14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☑ Other: Appendix A

1. The Amendment filed October 21, 2005 in response to the Office Action of April 21, 2005 is acknowledged and has been entered. Previously pending claim 2-5 and 13 have been canceled and new claims 14-16 have been added. Claims 14-16 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC ' 102

3. Claim 14 is rejected under 35 USC 102(b) as being anticipated by Yamamoto et al, Nature, 1986, 319:230-234.

The claim is drawn to an isolated polypeptide consisting of a portion of SEQ ID NO:2 consisting of at least residues 1021-1030. Given that the term "portion" is not defined in the specification, it is assumed for examination purposes that a portion of SEQ ID NO:2 consists of any or all contiguous amino acid residues of SEQ ID NO:2.

Yamamoto et al teach a polypeptide with 100% identity to SEQ ID NO:2, wherein the polypeptide is the entire portion of SEQ ID NO:2 and consists of at least residues 1021-1030 (see Sequence Search Report us-09-930-125-2.rup, result 1, Appendix A).

4. Claim 14 is rejected under 35 USC 102(e) as being anticipated by US2002/0177567.

The claim is drawn to an isolated polypeptide consisting of a portion of SEQ ID NO:2 consisting of at least residues 1021-1030.

US2002/0177567 teaches, as previously set forth, a polypeptide SEQ ID NO:5 which is a 59 amino acid residue fragment of the instantly claimed SEQ ID

NO:2 which consists of at least residues 1021-1030 of SEQ ID NO:2. All of the limitations of the claim are met. It is noted that Applicant has previously acknowledged on the record that the cited reference teaches an isolated polypeptide consisting of no more than amino acid residues 975-1209 of human Her-2/neu and comprises at least residues 1021-1030.

Claim Rejections - 35 USC ' 112

5. Claims 14 and 16, as they are drawn to SEQ ID NO:3 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are drawn to an isolated polypeptide consisting of a portion of SEQ ID NO:2 consisting of at least residues 1021-1030 (claim 14), consisting of residues 1021-1030 of SEQ ID NO:2, which is SEQ ID NO:3 (claim 16).

The specification teaches that the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response comprising administering a Her-2/neu polypeptide comprising the HLA-B44-restricted, naturally processed Her-2/neu epitope set forth in SEQ ID NO:3, wherein the patient may be afflicted with cancer and thus the cancer is treated or wherein the patient is considered at risk for such a disease and thus the patient is treated with the polypeptide prophylactically (p. 4, lines 21-29). Further, the specification teaches that the present invention is directed generally to compositions and their use in therapy of cancer (p. 8, lines 25-26) and provides polypeptides capable of eliciting T cells that are immunologically reactive with one

or more polypeptides described (p. 13, lines 12-19). T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide (p. 54, lines 18-22). T cells may be generated *in vitro* using known methods (p. 55, lines 10-15). The present invention concerns pharmaceutical compositions comprising polypeptides for administration for therapy and prevention of cancer. The pharmaceutical compositions of the invention may be used for the treatment of cancer, either by treatment of active disease or by prevention (p. 73, lines 21-30). The specification exemplifies the *in vitro* development and stimulation of a T-cell cell line that specifically recognizes full length SEQ ID NO:2 and the ICD fragment of SEQ ID NO:2, amino acids 676-1255 (p. 85, lines 24-28), wherein the response is restricted to HLA-B4402 (p. 86, line 5). Although the MCF-7 cell line naturally expresses low levels of Her-2/neu at the cell surface and is also HLA-B4402 positive, neither MCF-7 cells infected with AdV-SEQ ID NO:1 or parent cells were recognized by the T cell clone specific for HLAB4402 although fibroblasts transfected with the same construct were recognized (p, 87, lines 1-6). It was found that the T cell clone, named 17D5, recognizes SEQ ID NO:3 which corresponds to positions 1021-1030 in the Her-2/neu protein sequence of SEQ ID NO:2 (p. 87,lines 9-25). The specification exemplifies the partial protection of mice in an animal model wherein two weeks following what appears to be two immunizations with a polypeptide consisting of amino acids 676-1255 of SEQ ID NO:2, the mice were challenged with subcutaneous EL4 murine thymoma cells transfected with full length human Her-2/neu (apparently SEQ ID NO:1 which encodes SEQ ID NO:2). It was found that vaccination with the protein elicits a partially protective immune response (p. 90, lines 16-25). The nature of the

immune response responsible for mediating tumor protection appears to be T-cell dependent because depletion of the T-cells results in abrogation of the tumor protective response (para bridging pages 91-92). It was found that antibodies did not contribute to the observed protection despite the presence of substantial titers of anti-ICD antibody present in this sera. Taken together, these results suggest that antibody does not mediate the protection observed (p. 92, lines 8-20).

One cannot extrapolate the teaching of the specification to the enablement of the claims it appears that the only use contemplated for the claimed invention is as a therapeutic/pharmaceutical for the production of T cells useful in the treatment of HER-2/neu-associated diseases/cancer. In particular, it is clearly contemplated that the claimed peptide, an HLA restricted epitope recognized by T cell cline 17D5, will be used *in vivo* for stimulation of T cells contemplated in the specification for the treatment of cancer. Although the specification clearly teaches that antibodies against ICD portion of HER-2 neu are generated and one might expect to make antibodies against SEQ ID NO:3, for the reasons set forth below, this does not provide predictable enablement for the claimed invention.

As drawn to the contemplated cancer therapy with the claimed peptide for the production of T-cells against the cancer, Boon (Adv Can Res, 1992, 58:177-210, of record) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). Thus it would be unpredictable that administration of the peptide would be effective for eliciting an immune response, as a cancer vaccine, into

patients that already express a heavy load of the antigen would lead to an immune response against any tumor. Further, even if T-cells could be induced as contemplated, Sherman et al, (1998, Critical reviews in Immunol, 18(1-2): 47-54, of record) teach that self-tolerance may eliminate T cells that are capable of recognizing antigen epitopes with high avidity . In other words, only CTLs with low affinity are left, which would not be effective for tumor treatment *in vivo*. Smith (1994, (Clin Immunol, 41(4): 841-849, of record), teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limit the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484). In agreement, Boon, *Supra* teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Thus based on the teaching in the art and in the specification, one cannot predict that an adequate *in vivo* T cell response useful for immunotherapy could be induced by the claimed peptide in patients having tumor burden.

Further,as drawn to cancer therapy, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042, of record) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal

screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of *in vivo* evidence, no one skilled in the art would accept the assertion that the invention would function as contemplated and as claimed. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65, of record) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39, of record) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2).

Further, although not contemplated in the specification, as drawn to the use of antibodies generated against SEQ ID NO:3 in the contemplated cancer therapy, it is clear that antibodies to SEQ ID NO:3 would not be effective in the treatment protocols disclosed because the specification makes clear that sera against ICD (which would be expected to comprise antibodies against SEQ ID NO:3 if it were

an antibody epitope as well as a T cell epitope) which comprises SEQ ID NO:3 does not contribute to the therapy process.

In addition, although not contemplated in the specification, as drawn to the use of antibodies generated against SEQ ID NO:3 for binding to SEQ ID NO:2, even though the peptide claimed is 100% identical to a portion of SEQ ID NO:2, it would not be possible to determine with any predictability whether the antibodies produced from a polypeptide consisting of SEQ ID NO:3 actually bind to SEQ ID NO: 2. In particular, it cannot be predicted, given the information in the specification, whether the sequence is exposed on the surface of SEQ ID NO:2. Roitt et al, (1998, Immunology, 4th ed, Mosby, London, p.7.7-7.8) teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). Further, Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) teach that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). Furthermore, the specification does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary

and quarterary structure of a protein in a physiological situation. Further, although the specification defines SEQ ID NO:3 as a T cell epitope, as evidenced by Greenspan et al, defining antibody epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand (which is not here the case), then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). Since the specification has not identified which amino acids are critical or essential characteristics of the antibody epitope, it would not be predictable that the claimed peptide would in fact be a specific antibody epitope of SEQ ID NO:2 or that antibodies produced against the peptide would in fact bind to SEQ ID NO:2.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of ordinary skill in the art to predict that the invention would function as claimed and given the information in the art, no one of skill in the art would believe it more likely than not that the invention would function as contemplated with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

6. Claim 15 appears to be free of the art and allowable.

7. No claims allowed.

8. Applicant's amendment necessitated the new grounds of rejection.

Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Susan Ungar
Primary Patent Examiner
January 20, 2006

Appendix A

GenCore version 5.1.6
Copyright (c) 1993 - 2006 Compugen Ltd.

OM protein - protein search, using sw model

Run on: January 3, 2006, 11:05:32 ; Search time 259 Seconds
(without alignments)
3418.680 Million cell updates/sec

Title: US-09-930-125-2
Perfect score: 6815
Sequence: 1 MELAALCRWGLLLALLPPGA.....TFKGTPTAENPEYLGLDVPV 1255

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 2166443 seqs, 705528306 residues

Total number of hits satisfying chosen parameters: 2166443

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : UniProt_05.80:*
1: uniprot_sprot:*
2: uniprot_trembl:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	6815	100.0	1255	1	ERBB2_HUMAN	P04626 homo sapien
2	6304	92.5	1259	2	ERBB2_CANFA	O18735 canis famil
3	6007.5	88.2	1259	2	Q8K3F9_RAT	Q8k3f9 rattus norv
4	6003	88.1	1257	1	ERBB2_RAT	P06494 rattus norv
5	5993.5	87.9	1254	1	ERBB2_MESAU	Q60553 mesocricetu
6	5982.5	87.8	1305	2	Q6ZPE0_MOUSE	Q6zpe0 mus musculu
7	4216	61.9	881	2	Q8C0E7_MOUSE	Q8c0e7 m mus muscu
8	3514.5	51.6	1275	2	Q5EBY4_BRARE	Q5eby4 brachydanio
9	3256.5	47.8	711	2	Q80Y89_MOUSE	Q80y89 mus musculu
10	3172	46.5	1209	2	Q9QX70_RAT	Q9qx70 rattus norv
11	3167	46.5	1210	1	EGFR_HUMAN	P00533 homo sapien
12	3152.5	46.3	1209	2	Q8MIL8_PIG	Q8mil8 sus scrofa
13	3146	46.2	1210	1	EGFR_MOUSE	Q01279 mus musculu
14	3146	46.2	1210	2	Q5SVE8_MOUSE	Q5sve8 mus musculu
15	3143	46.1	1210	2	Q9EP98_MOUSE	Q9ep98 mus musculu
16	3045	44.7	1292	2	Q4PLA5_CHICK	Q4pla5 gallus gall
17	3036	44.5	1276	2	Q4PLA4_CHICK	Q4pla4 gallus gall
18	3006	44.1	1292	2	Q6UA28_RAT	Q6ua28 rattus norv
19	3004.5	44.1	1308	1	ERBB4_HUMAN	Q15303 homo sapien
20	3004	44.1	1308	2	Q6UA29_RAT	Q6ua29 rattus norv
21	2989	43.9	1308	1	ERBB4_RAT	Q62956 rattus norv
22	2988.5	43.9	1091	2	Q504U8_HUMAN	Q504u8 homo sapien
23	2986.5	43.8	1191	2	Q7SZF7_BRARE	Q7szf7 brachydanio
24	2977.5	43.7	1191	2	Q6VQA3_BRARE	Q6vqa3 brachydanio
25	2883.5	42.3	1209	2	Q6XJV8_XIPXI	Q6xjv8 xiphophorus
26	2857	41.9	1081	2	Q59FL8_HUMAN	Q59fl8 homo sapien
27	2758.5	40.5	1335	2	Q4RG29_TETNG	Q4rg29 tetraodon n
28	2758	40.5	1165	2	Q9YH40_XIPXI	Q9yh40 xiphophorus
29	2735.5	40.1	1137	2	Q9W6F6_CHICK	Q9w6f6 gallus gall
30	2724.5	40.0	1167	1	XMRK_XIPMA	P13388 xiphophorus
31	2620.5	38.5	1094	2	Q4RWY4_TETNG	Q4rwy4 tetraodon n
32	2441.5	35.8	1342	1	ERBB3_HUMAN	P21860 homo sapien
33	2438.5	35.8	1342	2	Q5RB22_PONPY	Q5rb22 pongo pygma
34	2408	35.3	1339	2	Q68J64_MOUSE	Q68j64 mus musculu
35	2370.5	34.8	1339	1	ERBB3_RAT	Q62799 rattus norv
36	2326	34.1	1328	2	P79754_FUGRU	P79754 fugu rubrip
37	2282	33.5	1429	2	Q5G254_BRARE	Q5g254 brachydanio
38	2209.5	32.4	1305	2	Q8AW81_BRARE	Q8aw81 brachydanio
39	2137.5	31.4	1344	2	Q4RW26_TETNG	Q4rw26 tetraodon n
40	2102	30.8	892	2	Q59EW4_HUMAN	Q59ew4 homo sapien
41	2066	30.3	1547	2	Q4RXV8_TETNG	Q4rxv8 tetraodon n
42	2062.5	30.3	1321	2	Q7PPN5_ANOGA	Q7ppn5 anopheles g
43	2059.5	30.2	1375	2	Q7PHU6_ANOGA	Q7phu6 anopheles g
44	2043.5	30.0	1433	2	Q9BIH9_ANOGA	Q9bih9 anopheles g
45	2024.5	29.7	435	2	Q6ZMM4_HUMAN	Q6zmm4 homo sapien

ALIGNMENTS

RESULT 1
ERBB2_HUMAN
ID ERBB2_HUMAN STANDARD; PRT; 1255 AA.
AC P04626; Q14256; Q6LDV1; Q9UMK4;
DT 13-AUG-1987 (Rel. 05, Created)
DT 13-AUG-1987 (Rel. 05, Last sequence update)
DT 13-SEP-2005 (Rel. 48, Last annotation update)
DE Receptor tyrosine-protein kinase erbB-2 precursor (EC 2.7.1.112)
DE (p185erbB2) (C-erbB-2) (NEU proto-oncogene) (Tyrosine kinase-type cell
DE surface receptor HER2) (MLN 19).
GN Name=ERBB2; Synonyms=HER2, NEU, NGL;
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae;
OC Homo.
OX NCBI_TaxID=9606;
RN [1]
RP NUCLEOTIDE SEQUENCE.
RX MEDLINE=86118663; PubMed=3002577;
RA Yamamoto T., Ikawa S., Akiyama T., Semba K., Nomura N., Miyajima N.,
RA Saito T., Toyoshima K.;
RT "Similarity of protein encoded by the human c-erb-B-2 gene to
RT epidermal growth factor receptor.";
RL Nature 319:230-234(1986).
RN [2]
RP NUCLEOTIDE SEQUENCE, AND VARIANT ALA-1170.
RX MEDLINE=86070181; PubMed=2999974;
RA Coussens L., Yang-Feng T.L., Liao Y.C., Chen E., Gray A., McGrath J.,
RA Seeburg P.H., Libermann T.A., Schlessinger J., Francke U.,
RA Levinson A., Ullrich A.;
RT "Tyrosine kinase receptor with extensive homology to EGF receptor
RT shares chromosomal location with neu oncogene.";
RL Science 230:1132-1139(1985).
RN [3]
RP NUCLEOTIDE SEQUENCE [GENOMIC DNA], AND VARIANTS CYS-452; VAL-655 AND
RP ALA-1170.
RA Rieder M.J., Livingston R.J., Daniels M.R., Montoya M.A., Chung M.-W.,
RA Miyamoto K.E., Nguyen C.P., Nguyen D.A., Poel C.L., Robertson P.D.,
RA Schackwitz W.S., Sherwood J.K., Witrak L.A., Nickerson D.A.;
RT "NIEHS-SNPs, environmental genome project, NIEHS ES15478, Department
RT of Genome Sciences, Seattle, WA (URL: http://egp.gs.washington.edu).";
RL Submitted (DEC-2002) to the EMBL/GenBank/DDBJ databases.
RN [4]
RP NUCLEOTIDE SEQUENCE OF 1-191.
RX MEDLINE=87286898; PubMed=3039351;
RA Tal M., King C.R., Kraus M.H., Ullrich A., Schlessinger J., Givol D.;
RT "Human HER2 (neu) promoter: evidence for multiple mechanisms for
RT transcriptional initiation.";
RL Mol. Cell. Biol. 7:2597-2601(1987).
RN [5]
RP NUCLEOTIDE SEQUENCE OF 737-1031.
RX MEDLINE=86016729; PubMed=2995967;
RA Semba K., Kamata N., Toyoshima K., Yamamoto T.;
RT "A v-erbB-related protooncogene, c-erbB-2, is distinct from the c-
RT "A v-erbB-related protooncogene, c-erbB-2, is distinct from the c-

```
RT   erbB-1/epidermal growth factor-receptor gene and is amplified in a
RT   human salivary gland adenocarcinoma.";
RL   Proc. Natl. Acad. Sci. U.S.A. 82:6497-6501(1985).
RN   [6]
RP   NUCLEOTIDE SEQUENCE OF 832-909.
RC   TISSUE=Mammary carcinoma;
RX   MEDLINE=85272597; PubMed=2992089;
RA   King C.R., Kraus M.H., Aaronson S.A.;
RT   "Amplification of a novel v-erbB-related gene in a human mammary
RT   carcinoma.";
RL   Science 229:974-976(1985).
RN   [7]
RP   NUCLEOTIDE SEQUENCE OF 1081-1245, AND VARIANT ALA-1170.
RX   MEDLINE=94000386; PubMed=8104414;
RA   Sarkar F.H., Ball D.E., Li Y.W., Crissman J.D.;
RT   "Molecular cloning and sequencing of an intron of Her-2/neu (ERBB2)
RT   gene.";
RL   DNA Cell Biol. 12:611-615(1993).
RN   [8]
RP   IDENTIFICATION IN A COMPLEX WITH PIK3C2A AND EGFR, IDENTIFICATION IN A
RP   COMPLEX WITH PIK3C2B AND EGFR, AND INTERACTION WITH PIK3C2B.
RX   PubMed=10805725;
RA   Arcaro A., Zvelebil M.J., Wallasch C., Ullrich A., Waterfield M.D.,
RA   Domin J.;
RT   "Class II phosphoinositide 3-kinases are downstream targets of
RT   activated polypeptide growth factor receptors.";
RL   Mol. Cell. Biol. 20:3817-3830(2000).
RN   [9]
RP   INTERACTION WITH PLXNB1.
RX   PubMed=15210733; DOI=10.1083/jcb.200312094;
RA   Swiercz J.M., Kuner R., Offermanns S.;
RT   "Plexin-B1/RhoGEF-mediated RhoA activation involves the receptor
RT   tyrosine kinase ErbB-2.";
RL   J. Cell Biol. 165:869-880(2004).
RN   [10]
RP   X-RAY CRYSTALLOGRAPHY (2.4 ANGSTROMS) OF 654-662 IN COMPLEX WITH HLA
RP   AND BETA-2 MICROGLOBULIN.
RX   MEDLINE=20062861; PubMed=10593938; DOI=10.1074/jbc.274.51.36422;
RA   Kuhns J.J., Batalia M.A., Yan S., Collins E.J.;
RT   "Poor binding of a HER-2/neu epitope (GP2) to HLA-A2.1 is due to a
RT   lack of interactions with the center of the peptide.";
RL   J. Biol. Chem. 274:36422-36427(1999).
RN   [11]
RP   X-RAY CRYSTALLOGRAPHY (2.52 ANGSTROMS) OF 23-629 IN COMPLEX WITH FAB.
RX   MEDLINE=22497871; PubMed=12610629; DOI=10.1038/nature01392;
RA   Cho H.-S., Mason K., Ramyar K.X., Stanley A.M., Gabelli S.B.,
RA   Denney D.W. Jr., Leahy D.J.;
RT   "Structure of the extracellular region of HER2 alone and in complex
RT   with the Herceptin Fab.";
RL   Nature 421:756-760(2003).
RN   [12]
RP   VARIANTS VAL-654 AND VAL-655.
RX   MEDLINE=93194196; PubMed=8095488;
RA   Ehsani A., Low J., Wallace R.B., Wu A.M.;
RT   "Characterization of a new allele of the human ERBB2 gene by allele-
RT   specific competition hybridization.";
RL   Genomics 15:426-429(1993).
CC   -!- FUNCTION: Essential component of a neuregulin-receptor complex,
CC       althought neuregulins do not interact with it alone. GP30 is a
CC       potential ligand for this receptor. Not activated by EGF, TGF-
CC       alpha and amphiregulin.
CC   -!- CATALYTIC ACTIVITY: ATP + a protein tyrosine = ADP + a protein
CC       tyrosine phosphate.
CC   -!- SUBUNIT: Heterodimer with each of the other ERBB receptors
CC       (Potential). Interacts with PRKCABP (By similarity). Binds PLXNB1.
CC       Part of a complex with EGFR and either PIK3C2A or PIK3C2B. May
CC       interact with PIK3C2B when phosphorylated on Tyr-1196.
CC   -!- SUBCELLULAR LOCATION: Type I membrane protein.
CC   -!- PTM: Ligand-binding increases phosphorylation on tyrosine residues
CC       (By similarity).
CC   -!- POLYMORPHISM: There are fours alleles due to the variations in
CC       positions 654 and 655. Allele B1 (Ile-654/Ile-655) has a frequency
CC       of 0.782; allele B2 (Ile-654/Val-655) has a frequency of 0.206;
CC       allele B3 (Val-654/Val-655) has a frequency of 0.012.
CC   -!- SIMILARITY: Belongs to the Tyr protein kinase family. EGF receptor
CC       subfamily.
CC   ---------------------------------------------------------------------
CC   This Swiss-Prot entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use as long as its content is in no way modified and this statement is not
CC   removed.
CC   ---------------------------------------------------------------------
DR   EMBL; M11767; AAA35808.1; -; Genomic_DNA.
DR   EMBL; M11761; AAA35808.1; JOINED; Genomic_DNA.
DR   EMBL; M11762; AAA35808.1; JOINED; Genomic_DNA.
DR   EMBL; M11763; AAA35808.1; JOINED; Genomic_DNA.
DR   EMBL; M11764; AAA35808.1; JOINED; Genomic_DNA.
DR   EMBL; M11765; AAA35808.1; JOINED; Genomic_DNA.
DR   EMBL; M11766; AAA35808.1; JOINED; Genomic_DNA.
DR   EMBL; M11730; AAA75493.1; -; mRNA.
DR   EMBL; M12036; AAA35978.1; -; Genomic_DNA.
DR   EMBL; AY208911; AAO18082.1; -; Genomic_DNA.
DR   EMBL; X03363; CAA27060.1; -; mRNA.
DR   EMBL; M16792; AAA58637.1; -; Genomic_DNA.
DR   EMBL; M16789; AAA58637.1; JOINED; Genomic_DNA.
DR   EMBL; M16790; AAA58637.1; JOINED; Genomic_DNA.
DR   EMBL; M16791; AAA58637.1; JOINED; Genomic_DNA.
DR   EMBL; L29395; AAA35809.1; -; Genomic_DNA.
DR   EMBL; M95667; AAC37531.1; -; Unassigned_DNA.
DR   PIR; A24571; A24571.
DR   PDB; 1N8Z; X-ray; C=23-629.
DR   PDB; 1OVC; Model; A=737-1031.
DR   PDB; 1S78; X-ray; A/B=23-646.
DR   Ensembl; ENSG00000141736; Homo sapiens.
DR   HGNC; HGNC:3430; ERBB2.
DR   MIM; 164870; -.
DR   GO; GO:0016021; C:integral to membrane; NAS.
DR   GO; GO:0005886; C:plasma membrane; NAS.
DR   GO; GO:0005006; F:epidermal growth factor receptor activity; NAS.
DR   GO; GO:0043125; F:ErbB-3 class receptor binding; TAS.
DR   GO; GO:0046982; F:protein heterodimerization activity; NAS.
DR   GO; GO:0004716; F:receptor signaling protein tyrosine kinase . . .; TAS.
DR   GO; GO:0008283; P:cell proliferation; TAS.
DR   GO; GO:0007507; P:heart development; TAS.
DR   GO; GO:0030879; P:mammary gland development; TAS.
DR   GO; GO:0007399; P:neurogenesis; TAS.
DR   GO; GO:0048015; P:phosphoinositide-mediated signaling; NAS.
DR   GO; GO:0006468; P:protein amino acid phosphorylation; TAS.
DR   GO; GO:0045765; P:regulation of angiogenesis; NAS.
DR   GO; GO:0007169; P:transmembrane receptor protein tyrosine kin. . .; NAS.
DR   InterPro; IPR000494; EGFR_L.
DR   InterPro; IPR006211; Furin-like.
DR   InterPro; IPR006212; Furin_repeat.
DR   InterPro; IPR000719; Prot_kinase.
DR   InterPro; IPR001245; Tyr_pkinase.
DR   InterPro; IPR008266; Tyr_pkinase_AS.
DR   InterPro; IPR004019; YLP_motif.
DR   Pfam; PF00757; Furin-like; 1.
DR   Pfam; PF01030; Recep_L_domain; 2.
DR   Pfam; PF02757; YLP; 2.
DR   PRINTS; PR00109; TYRKINASE.
DR   ProDom; PD000001; Prot_kinase; 1.
DR   SMART; SM00261; FU; 3.
DR   SMART; SM00219; TyrKc; 1.
DR   PROSITE; PS00107; PROTEIN_KINASE_ATP; 1.
DR   PROSITE; PS50011; PROTEIN_KINASE_DOM; 1.
DR   PROSITE; PS00109; PROTEIN_KINASE_TYR; 1.
KW   3D-structure; ATP-binding; Glycoprotein; Kinase; Multigene family;
KW   Nucleotide-binding; Phosphorylation; Polymorphism; Receptor; Signal;
KW   Transferase; Transmembrane; Tyrosine-protein kinase.
FT   SIGNAL       1    21       Potential.
FT   CHAIN       22  1255       Receptor tyrosine-protein kinase erbB-2.
FT   TOPO_DOM    22   652       Extracellular (Potential).
FT   TRANSMEM   653   675       Potential.
FT   TOPO_DOM   676  1255       Cytoplasmic (Potential).
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FT   DOMAIN      720    987       Protein kinase.
FT   NP_BIND     726    734       ATP (By similarity).

  Query Match           100.0%;  Score 6815;  DB 1;  Length 1255;
  Best Local Similarity  100.0%;  Pred. No. 0;
  Matches 1255;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNL 60
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNL 60

Qy         61 ELTYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNG 120
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 ELTYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNG 120

Qy        121 DPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLA 180
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 DPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLA 180

Qy        181 LTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCCHEQC 240
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 LTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCCHEQC 240

Qy        241 AAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACP 300
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Db        241 AAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACP 300

Qy        301 YNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSAN 360
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSAN 360

Qy        361 IQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLP 420
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 IQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLP 420

Qy        421 DLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLALIHHNTHLCFVHTV 480
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 DLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLALIHHNTHLCFVHTV 480

Qy        481 PWDQLFRNPHQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVNCSQFLRGQEC 540
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Db        481 PWDQLFRNPHQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVNCSQFLRGQEC 540

Qy        541 VEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARC 600
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Db        541 VEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARC 600

Qy        601 PSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTSIISAVVG 660
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Db        601 PSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTSIISAVVG 660

Qy        661 ILLVVVLGVVFGILIKRRQQKIRKYTMRRLLQETELVEPLTPSGAMPNQAQMRILKETEL 720
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Db        661 ILLVVVLGVVFGILIKRRQQKIRKYTMRRLLQETELVEPLTPSGAMPNQAQMRILKETEL 720

Qy        721 RKVKVLGSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSP 780
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 RKVKVLGSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSP 780

Qy        781 YVSRLLGICLTSTVQLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKGMSYLEDVR 840
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Db        781 YVSRLLGICLTSTVQLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKGMSYLEDVR 840

Qy        841 LVHRDLAARNVLVKSPNHVKITDFGLARLLDIDETEYHADGGKVPIKWMALESILRRRFT 900
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 LVHRDLAARNVLVKSPNHVKITDFGLARLLDIDETEYHADGGKVPIKWMALESILRRRFT 900

Qy        901 HQSDVWSYGVTVWELMTFGAKPYDGIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWM 960
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 HQSDVWSYGVTVWELMTFGAKPYDGIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWM 960

Qy        961 IDSECRPRFRELVSEFSRMARDPQRFVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDA 1020
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Db        961 IDSECRPRFRELVSEFSRMARDPQRFVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDA 1020

Qy       1021 EEYLVPQQGFFCPDPAPGAGGMVHHRHRSSSTRSGGGDLTLGLEPSEEEAPRSPLAPSEG 1080
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021 EEYLVPQQGFFCPDPAPGAGGMVHHRHRSSSTRSGGGDLTLGLEPSEEEAPRSPLAPSEG 1080

Qy       1081 AGSDVFDGDLGMGAAKGLQSLPTHDPSPLQRYSEDPTVPLPSETDGYVAPLTCSPQPEYV 1140
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Db       1081 AGSDVFDGDLGMGAAKGLQSLPTHDPSPLQRYSEDPTVPLPSETDGYVAPLTCSPQPEYV 1140

Qy       1141 NQPDVRPQPPSPREGPLPAARPAGATLERPKTLSPGKNGVVKDVFAFGGAVENPEYLTPQ 1200
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1141 NQPDVRPQPPSPREGPLPAARPAGATLERPKTLSPGKNGVVKDVFAFGGAVENPEYLTPQ 1200

Qy       1201 GGAAPQPHPPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVPV 1255
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1201 GGAAPQPHPPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVPV 1255


RESULT 2
ERBB2_CANFA
ID   ERBB2_CANFA     STANDARD;      PRT;  1259 AA.
AC   O18735;
DT   25-OCT-2004 (Rel. 45, Created)
DT   25-OCT-2004 (Rel. 45, Last sequence update)
DT   13-SEP-2005 (Rel. 48, Last annotation update)
DE   Receptor tyrosine-protein kinase erbB-2 precursor (EC 2.7.1.112)
DE   (p185erbB2) (C-erbB-2).
GN   Name=ERBB2;
OS   Canis familiaris (Dog).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Laurasiatheria; Carnivora; Fissipedia; Canidae;
OC   Canis.
OX   NCBI_TaxID=9615;
RN   [1]
RP   NUCLEOTIDE SEQUENCE.
RC   TISSUE=Mammary gland;
RA   Yokota H.;
RT   "cDNA cloning of erbB-2 from canine mammary gland.";
RL   Submitted (OCT-1997) to the EMBL/GenBank/DDBJ databases.
CC   -!- FUNCTION: Essential component of a neuregulin-receptor complex,
CC       althought neuregulins do not interact with it alone. GP30 is a
CC       potential ligand for this receptor. Not activated by EGF, TGF-
CC       alpha and amphiregulin (By similarity).
CC   -!- CATALYTIC ACTIVITY: ATP + a protein tyrosine = ADP + a protein
CC       tyrosine phosphate.
CC   -!- SUBUNIT: Heterodimer with each of the other ERBB receptors
CC       (Potential). Interacts with PRKCABP. Binds PLXNB1. Part of a
CC       complex with EGFR and either PIK3C2A or PIK3C2B. May interact with
CC       PIK3C2B when phosphorylated on Tyr-1200 (By similarity).
CC   -!- SUBCELLULAR LOCATION: Type I membrane protein.
CC   -!- PTM: Ligand-binding increases phosphorylation on tyrosine residues
CC       (By similarity).
CC   -!- SIMILARITY: Belongs to the Tyr protein kinase family. EGF receptor
CC       subfamily.
CC   ---------------------------------------------------------------------
CC   This Swiss-Prot entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use as long as its content is in no way modified and this statement is not
CC   removed.
CC   ---------------------------------------------------------------------
DR   EMBL; AB008451; BAA23127.1; -; mRNA.
DR   HSSP; P04626; 1N8Z.
DR   SMR; O18735; 23-628.
DR   Ensembl; ENSCAFG00000016351; Canis familiaris.
DR   InterPro; IPR000494; EGFR_L.
DR   InterPro; IPR006211; Furin-like.
DR   InterPro; IPR006212; Furin_repeat.
DR   InterPro; IPR000719; Prot_kinase.
DR   InterPro; IPR001245; Tyr_pkinase.
DR   InterPro; IPR008266; Tyr_pkinase_AS.
DR   InterPro; IPR004019; YLP_motif.
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